Antibiotic treatment for pneumonia complicating stroke: Recommendations from the pneumonia in stroke consensus (PISCES) group

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Abstract: Purpose The microbiological aetiology of pneumonia complicating stroke is poorly characterised. In this second Pneumonia in Stroke ConsEnsuS statement, we propose a standardised approach to empirical antibiotic therapy in pneumonia complicating stroke, based on likely microbiological aetiology, to improve antibiotic stewardship. Methods Systematic literature searches of multiple databases were undertaken. An evidence review and a round of consensus consultation were completed prior to a final multi-disciplinary consensus meeting in September 2017, held in Barcelona, Spain. Consensus was approached using a modified Delphi technique and defined a priori as 75% agreement between the consensus group members. Findings: No randomised trials to guide antibiotic treatment of pneumonia complicating stroke were identified. Consensus was reached for the following: (1) Stroke-associated pneumonia may be caused by organisms associated with either community-acquired or hospital-acquired pneumonia; (2) Treatment for early stroke-associated pneumonia (<72 h of stroke onset) should cover community-acquired pneumonia organisms; (3) Treatment for late stroke-associated pneumonia (72 h and within seven days of stroke onset) should cover community-acquired pneumonia organisms plus coliforms +/− Pseudomonas spp. if risk factors; (4) No additional antimicrobial cover is required for patients with dysphagia or aspiration; (5) Pneumonia occurring after seven days from stroke onset should be treated as for hospital-acquired pneumonia; (6) Treatment should continue for at least seven days for each of these scenarios. Discussion Consensus recommendations for antibiotic treatment of the spectrum of pneumonia complicating stroke are proposed. However, there was limited evidence available to formulate consensus on choice of specific antibiotic class for pneumonia complicating stroke. Conclusion Further studies are required to inform evidence-based treatment of stroke-associated pneumonia including randomised trials of antibiotics and validation of candidate biomarkers.

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Antibiotic treatment for pneumonia complicating stroke: Recommendations from the pneumonia in stroke consensus (PISCES) group

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Abstract

Purpose: The microbiological aetiology of pneumonia complicating stroke is poorly characterised. In this second Pneumonia in Stroke ConsEnsuS statement, we propose a standardised approach to empirical antibiotic therapy in pneumonia complicating stroke, based on likely microbiological aetiology, to improve antibiotic stewardship.

Methods: Systematic literature searches of multiple databases were undertaken. An evidence review and a round of consensus consultation were completed prior to a final multi-disciplinary consensus meeting in September 2017, held in Barcelona, Spain. Consensus was approached using a modified Delphi technique and defined a priori as 75% agreement between the consensus group members.

Findings: No randomised trials to guide antibiotic treatment of pneumonia complicating stroke were identified. Consensus was reached for the following: (1) Stroke-associated pneumonia may be caused by organisms associated with either community-acquired or hospital-acquired pneumonia; (2) Treatment for early stroke-associated pneumonia ($<$72 h of stroke onset) should cover community-acquired pneumonia organisms; (3) Treatment for late stroke-associated pneumonia ($\geq$72 h and within seven days of stroke onset) should cover community-acquired pneumonia organisms plus coliforms +/− *Pseudomonas spp*. if risk factors; (4) No additional antimicrobial cover is required for patients with dysphagia or aspiration; (5) Pneumonia occurring after seven days from stroke onset should be treated as for hospital-acquired pneumonia; (6) Treatment should continue for at least seven days for each of these scenarios.

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Discussion: Consensus recommendations for antibiotic treatment of the spectrum of pneumonia complicating stroke are proposed. However, there was limited evidence available to formulate consensus on choice of specific antibiotic class for pneumonia complicating stroke.
Conclusion: Further studies are required to inform evidence-based treatment of stroke-associated pneumonia including randomised trials of antibiotics and validation of candidate biomarkers.

Keywords
Stroke, stroke-associated pneumonia, post-stroke pneumonia, antibiotics, treatment

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Introduction

Pneumonia is a serious and common complication of stroke which is associated with significantly increased healthcare costs, poor functional outcome and mortality.[1–3] The Pneumonia in Stroke ConsEnSuS (PISCES) group was formed as a multi-disciplinary initiative to address uncertainties in the diagnosis, prevention and treatment of pneumonia complicating stroke, and to identify key research priorities. The first PISCES consensus focused on terminology and diagnostic criteria for the spectrum of lower respiratory tract infections, including the proposed definition and operational criteria for stroke-associated pneumonia (SAP).[4]

In clinical practice, immediate treatment of pneumonia complicating stroke is recommended once suspected or diagnosed.[5,6] Initial choice of antibiotics is often broad spectrum, being either clinician dependent or guided by various international guidelines for community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) or aspiration pneumonia.[5–7] There is, however, substantial variation in antibiotic prescription practices across healthcare systems,[7] which could have implications for clinical outcomes. Determining microbiological aetiology in pneumonia complicating stroke is challenging given the difficulty in obtaining sputum samples in non-ventilated stroke patients and poor diagnostic sensitivity of other available culture specimens, which may limit definitive antibiotic treatment based on microbial mechanisms independent of their antimicrobial coverage, for example anti-inflammatory and immunomodulatory effects.[11]

Choice of antibiotics for treatment of pneumonia complicating stroke may therefore have important implications for antibiotic stewardship and clinical outcomes in clinical practice. In this second PISCES group consensus process (PISCES-2), we aimed to formulate antibiotic treatment recommendations for pneumonia complicating stroke, and to identify areas for future research.

Methods

Membership of the PISCES group and protocol development

The PISCES group was originally convened by the Chair (C.J.S) based on collective multidisciplinary expertise across the spectrum of SAP, pneumonia, respiratory medicine, stroke neurology, stroke unit and neurocritical care management, infectious diseases, clinical microbiology, systematic review, and clinical guidelines. For this consensus process, the PISCES group included 18 clinicians with representation from the UK, Germany, Spain, Italy, Netherlands and Switzerland. The protocol for the present study was drafted by the chair in conjunction with the co-chairs (A.M and J.M) and reviewed by the group to further define the objectives, methodology, and statements for

Table 1. Summary of PISCES-2 consensus recommendation for antibiotic treatment of pneumonia complicating stroke.

Bacterial species in SAP are likely to be those in hospitalised CAP or HAP
Antibiotic treatment should be initiated as soon as possible after diagnosis of probable or definite SAP, and within 4 h (within 1 h if sepsis or septic shock)
For early SAP (<72 h of stroke onset) antibiotic coverage of CAP organisms is recommended
For late SAP (≥72 h and ≤ 7 d of stroke onset) antibiotic coverage of CAP organisms plus coverage of coliforms (and *P. aeruginosa* if risk factors) is recommended
For pneumonia developing > 7 days after stroke onset, HAP guidelines should be followed
No additional anti-microbial coverage is required if aspiration is suspected or confirmed For patients at risk for drug-resistant organisms, admitted from health care facilities or with pre-existing immune-suppression, additional antibiotic cover for MRSA, ESBL-producing enteric bacteria (*E. coli, K. pneumoniae*), *P. aeruginosa* or *Acinetobacter* species are recommended as clinically indicated and in conjunction with other recommendations for treatment of SAP and HAP
Choice of antibiotic should also be guided by available route, local antibiotic resistance patterns and other criteria with reference to societal guidelines
Pneumonia occurring in the community and clearly preceding stroke admission should be treated as hospitalised CAP including consideration of atypical organisms
Further research is needed to address uncertainties of microbial etiologies, choice of antibiotic classes (and agents), timing and duration of treatment and role of biomarkers in SAP treatment

SAP: stroke-associated pneumonia; CAP: community-acquired pneumonia; HAP: hospital-acquired pneumonia; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended spectrum beta lactamase

complicating stroke was undertaken and has been reported previously.[8] A second systematic literature search sought to identify randomised controlled trials (RCTs) of antibiotic treatment for pneumonia complicating stroke (Table I in the online-only Data Supplement) in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [12] Briefly, published studies of ischemic stroke, intracerebral haemorrhage (ICH), or both, involving antibiotic treatment of pneumonia were independently screened for eligibility (Table II in the online-only Data Supplement) by A.K.K and C.J.S using the study title and abstract. Online trials registries (ISRCTN Registry, ClinicalTrials.gov, ICTRP Portal) were also searched for registered ongoing or recently completed, unpublished RCTs. A summary of currently available antibiotic classes in clinical practice, antimicrobial activities and antibiotic stewardship issues (including antibiotic resistance) was provided by the study microbiologist (A.R.J). Review of specialist societal recommendations for CAP, HAP and aspiration pneumonia was also undertaken, with reference to antibiotic classes used, led by A.K.K and the study infectious diseases specialist (J.G).

group meeting along with summaries of antibiotic classes, sensitivities, resistance and societal recommendations for CAP, HAP and aspiration pneumonia in Barcelona, Spain on 27 September 2017. Consensus was approached using a modified Delphi technique and defined a priori as 75% agreement between the consensus group members.[13]

Findings

The main recommendations of the consensus process are summarised in Table 1 and Figure 1. The consensus statements considered, including the online survey results and final consensus opinions are summarised in Table III in the online-only supplement.

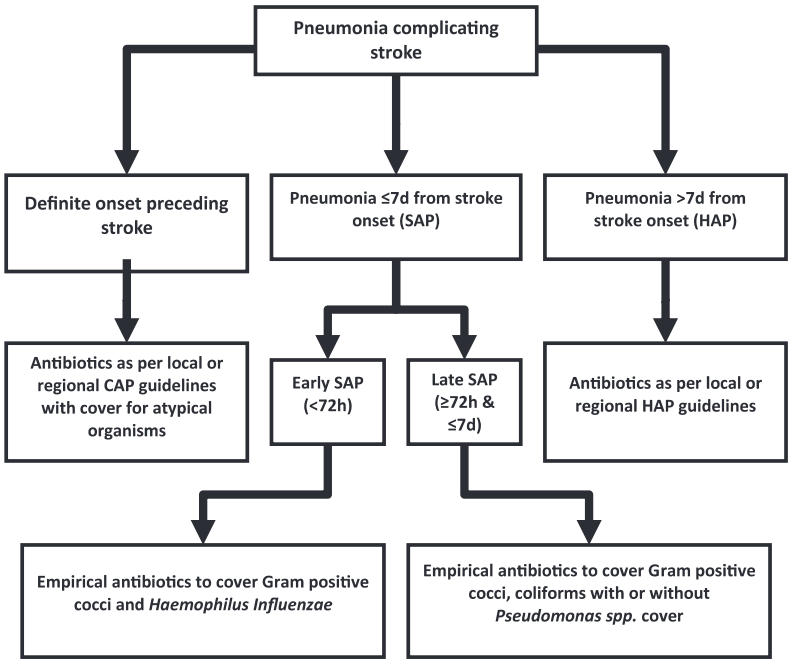
Remit and scope of the consensus

The requirement for consensus-based guidelines for the empirical antibiotic treatment of pneumonia complicating stroke (ischaemic stroke and ICH) was agreed by preliminary consensus. Agreement was also reached by preliminary consensus that the main focus of these recommendations should be SAP, defined in a previous publication as pneumonia within seven days of stroke

Table 2. Initial empirical antibiotic choice for hospitalised CAP and aspiration pneumonia (previously healthy individuals without known *S. aureus* resistance and prior to pathogen isolation and susceptibility testing).[5,6]

European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases on management of hospitalised CAP in adults	Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of hospitalised CAP in Adults
Inpatients, non-ICU treatment Aminopenicillin ± macrolide **OR** Aminopenicillin/ β-lactamase inhibitor ± macrolide **OR** Non-antipseudomonal cephalosporin **OR** Cefotaxime or Ceftriaxone ± macrolide OR Levofloxacin **OR** Moxifloxacin **OR** penicillin G ± macrolide **Aspiration pneumonia** oral or parenteral β-lactam/ β-lactamase inhibitor **OR** Clindamycin **OR** parenteral cephalosporin + oral Metronidazole **OR** Moxifloxacin	Inpatients, non-ICU treatment Respiratory fluoroquinolone OR β-lactam plus macrolide **Risk factors for *Pseudomonas aeruginosa*** An anti-pneumococcal, antipseudomonal β-lactam (Piperacillin, Tazobactam, Cefepime,Imipenem, or Meropenem) + either Ciprofloxacin or Levofloxacin **OR** The above β-lactam + aminoglycoside and Azithromycin **OR** The above β-lactam + an aminoglycoside and an anti-pneumococcal fluoroquinolone (for penicillin-allergic patients, substitute Aztreonam for above β-lactam)

CAP: community acquired pneumonia; ICU: intensive-care unit.



Decision on parenteral antibiotics should be made in conjunction with clinical decision on severity of pneumonia with step down to oral antibiotics guided by clinical response

Table 3. Specialist societal guidelines for HAP/VAP.[14,15]

European Respiratory Society, European Society of Intensive Care Medicine, European Society for Clinical Microbiology and Infectious Diseases, Asociación Latinoamericana del Tórax on management of HAP in adults	Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of HAP in Adults
Low-risk patients (without septic shock, with no other risk factors for MDR pathogens and those who are not in hospitals with a high background rate of resistant pathogens and with low risk of mortality)	Not at high risk of mortality and no factors increasing likelihood of MRSA
Narrow-spectrum antibiotics (ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin) in patients with suspected low risk of resistance and early-onset HAP/VAP	Piperacillin + Tazobactam **OR** Cefepime **OR** Levofloxacin **OR** Imipenem/ Meropenem
High-risk patients (in patients with suspected early-onset HAP/VAP who are in septic shock, in patients who are in hospitals with a high background rate of resistant pathogens present in local microbiological data and in patients with other (non-classic) risk factors for MDR pathogens)	Not at high risk of mortality but with factors increasing likelihood of MRSA One of the following: Piperacillin + Tazobactam **OR** Cefepime **OR** Levofloxacin **OR** Imipenem/ Meropenem **OR** Aztreonam **PLUS** Vancomycin **OR** Linezolid
Broad-spectrum empiric antibiotic therapy targeting *Pseudomonas aeruginosa* and extended-spectrum β-lactamase producing organisms	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days Two of the following (avoid 2 β-Lactams) Piperacillin + Tazobactam **OR** Cefepime **OR** Levofloxacin **OR** Imipenem/ Meropenem **OR** Aztreonam **OR** Amikacin/Gentamicin/Tobramycin **PLUS** Vancomycin **OR** Linezolid

HAP: hospital acquired pneumonia; VAP: ventilator associated pneumonia; MDR: multiple-drug resistant; MRSA: methiciliin-resistant *Staphylococcus aureus*.

Recommendations

The guidelines apply mainly to SAP (pneumonia ≤ 7 days after stroke onset). Other specialist societal guidelines for HAP[11,12] *should be applied beyond seven days after stroke onset.*

Microbiological aetiology of SAP and microbiological testing

A systematic review of 15 studies of patients with pneumonia complicating stroke suggested that aerobic Gram negative bacilli (38%) and Gram positive cocci (16%) were most frequently isolated among positive cultures.[8] Commonly isolated bacterial species included *Enterobacteriaceae* (21.8%: *Klebsiella pneumoniae*, 12.8% and *Escherichia coli*, 9%), *Staphylococcus*

there were several limitations, including significant heterogeneity and inability to separate causal from commensal bacteria. There were insufficient data to identify the relative contributions of particular bacteria in relation to the timing of onset of SAP. Anaerobes, often thought to be one of the primary bacterial groups causing aspiration pneumonia, were either not detected or reported in any of the studies. None of the studies in the review used modern molecular diagnostic techniques such as multiplex polymerase chain reaction (PCR) platforms to detect multiple bacterial species, respiratory viruses or atypical organisms. Difficulty in consistently obtaining sputum culture samples in non-ventilated stroke patients was acknowledged. Consensus was reached that bacterial species implicated in SAP may overlap with those associated with either CAP or HAP. It was acknowledged that evi-

example, sputum cultures) should be made where feasible in stroke patients for targeted antibiotic treatment.

Antibiotic treatment considerations for SAP based on presumed microbial aetiology

Based on the available evidence for bacterial species,[8] consensus was reached that antibiotics for SAP should cover Gram positive cocci, coliforms and, when risk factors are present, *Pseudomonas* (see below). Empirical antibiotic treatment for early SAP (<72 h of stroke onset) to cover CAP pathogens was recommended and additional cover for Gram negative bacilli was agreed from $\geq$ 72 h and $\leq$ 7 days (late SAP) of stroke symptom onset. Consensus was reached that in cases of SAP where pneumonia was diagnosed in the community preceding stroke onset, then it would be reasonable to treat for CAP with antibiotics including cover for atypical organisms. The available literature for microbial aetiology of aspiration pneumonia was considered.[17] Aspiration pneumonia has previously been regarded as being predominantly due to anaerobes (e.g. *Bacteroides spp.*, *Fusobacterium spp.*) but more recent studies have reported less contribution from anaerobes (<20%) with greater prevalence of *S. aureus*, Gram negative bacilli and aerobic organisms.[18–20] This has been reflected by specialist societal antibiotic recommendations for aspiration pneumonia (Table 2).

Recommendations

1. *For patients with pneumonia manifesting after admission and < 72 h of stroke onset (Early SAP) and without special circumstances (see below), empirical antibiotics to cover typical CAP pathogens i.e. Gram positive cocci in addition to Haemophilus influenzae and Moraxella catarrhalis are recommended.*
2. *For patients with pneumonia manifesting $\geq$ 72 h, but before seven days of stroke onset (Late SAP) and without special circumstances (see below), empirical antibiotics to cover coliforms (with or without coverage of P. aeruginosa, if risk factors*) in addition to covering pathogens for CAP are recommended.*
3. *No additional anti-microbial coverage is required if bronchiectasis), mechanical ventilation, prior antibiotic therapy.*[6]

Special circumstances

Special circumstances, including patients with pre-existing immune suppression, at risk from multidrug-resistant organisms* [21] or patients admitted from other healthcare facilities or institutions were considered. In these circumstances, additional cover for Methicillin-resistant *S. aureus* (MRSA) in addition to antibiotic coverage of other Gram negative bacteria (such as *P. aeruginosa*) should be used in conjunction with the above recommendations. Consensus was reached that local or societal guidelines for VAP be followed for pneumonia after seven days of stroke onset in mechanically ventilated patients.[14,15] As dysphagia is a common complication of stroke, parenteral antibiotics were suggested as initial cover for SAP if patients were placed nil orally. Early step-down to appropriate oral antibiotics should be considered once enteral feeding is secured and the patient has achieved stability. Patients who develop recurrent pneumonia in hospital following an initial antibiotic course for SAP or HAP should be treated with antibiotics to cover HAP organisms based on liaison with local microbiology or infectious diseases expertise and policy.

Recommendations

1. *For stroke patients at risk for drug-resistant organisms*, admitted from health care facilities or with pre-existing immune-suppression, additional antibiotic cover for MRSA, Extended Spectrum Beta Lactamase (ESBL)-producing enteric bacteria (E. coli, K. pneumoniae), P. aeruginosa or Acinetobacter species should be considered as clinically indicated and in conjunction with local patterns of antibiotic resistance and other recommendations for treatment of SAP and HAP.*
2. *Pneumonia in stroke patients complicated by mechanical ventilation should follow guidelines for SAP (pneumonia $\leq$ 7 days of stroke onset) or VAP (>7 days after stroke onset) guidelines, respectively.*
3. *Initial parenteral antibiotics are recommended in dys-*

additionally if VAP: ≥5 days of prior hospitalisation, preceding acute respiratory distress syndrome, preceding acute renal replacement, septic shock).[21]

Pneumonia severity and timing of initiation of antibiotics

There is currently no evidence to support the routine use of prophylactic antibiotics to prevent development of SAP, either in unselected stroke populations or those considered at higher risk placed nil orally.[22] Furthermore, the STRoke Adverse outcome is associated WIth NoSocomial Infections (STRAWINSKI) study did not support the use of procalcitonin-guided antibiotic initiation for pneumonia or other infections complicating stroke.[23] The appropriate timing of initiation of antibiotics in probable or definite SAP[4] therefore remains uncertain although immediate antibiotic treatment (and within 4 h, or within 1 h if septic shock) was considered acceptable and agreed in line with recommendations from the European Respiratory Society and National Institute of Clinical Excellence (NICE) guidelines.[5,14,16] The group acknowledged that there were currently no published severity scores derived and validated in patients with SAP. Consensus was reached that the utility of pneumonia severity scores developed in CAP (for example CURB -65 and Pneumonia Severity Index [PSI]) requires evaluation in patients with SAP.[5,6]

Recommendations

1. *Start antibiotic therapy as soon as possible and certainly within 4 h (within 1 h if sepsis or septic shock) in all patients with probable or definite SAP.*[4]
2. *There are currently no validated severity scores for SAP and existing pneumonia severity scores for (e.g. CURB-65or PSI) require evaluation in patients with SAP.*

Which antibiotics should be used in SAP and for how long?

Evidence was considered regarding currently available antibiotic classes and mechanism of action, antibiotic supplement). In our recent systematic review,[8] the choice of antibiotics used to treat pneumonia complicating stroke was documented in only four (24%) studies and was determined by local hospital policy. Antibiotics commonly included β-lactam antibiotics (including ureidopenicillin and 2nd/3rd generation cephalosporins), with or without β-lactamase inhibitors and 2nd/3rd generation fluoroquinolones and were always initiated prior to obtaining antibiotic sensitivities.

Consensus was reached that there was insufficient evidence to recommend any particular antibiotic agent(s) or classes of antibiotic for treatment of SAP, and that evaluation of antibiotic treatment of SAP was a research priority. Penicillin plus β-lactamase inhibitors were preferred by the majority of the group for patients with SAP, aspiration pneumonia and recurrent pneumonia complicating stroke. Local patterns of antimicrobial resistance should be considered when determining appropriate empirical therapy. Consensus was also achieved for recommending that duration of antibiotic treatment should be guided by clinical response and should be for at least seven days. It was acknowledged that the role of biomarkers to guide treatment duration was unknown and further research was needed in this regard.

Recommendations

1. *Choice of initial empirical antibiotics for early SAP (predominantly Gram positive cocci) may commonly include β-lactams and macrolides or respiratory fluoroquinolones.*
2. *Choice of initial empirical antibiotic therapy for late SAP should additionally cover Gram negative bacteria, with or without Pseudomonas cover, and may commonly include β-lactams (e.g. penicillin plus β-lactamase inhibitor, 3rd or 4th generation cephalosporins, monobactams), fluoroquinolones or aminoglycosides.*
3. *Local patterns of antimicrobial resistance should be considered when determining appropriate empirical therapy.*
4. *Antibiotic treatment should be for at least seven days and guided by clinical response, in the absence of val-*

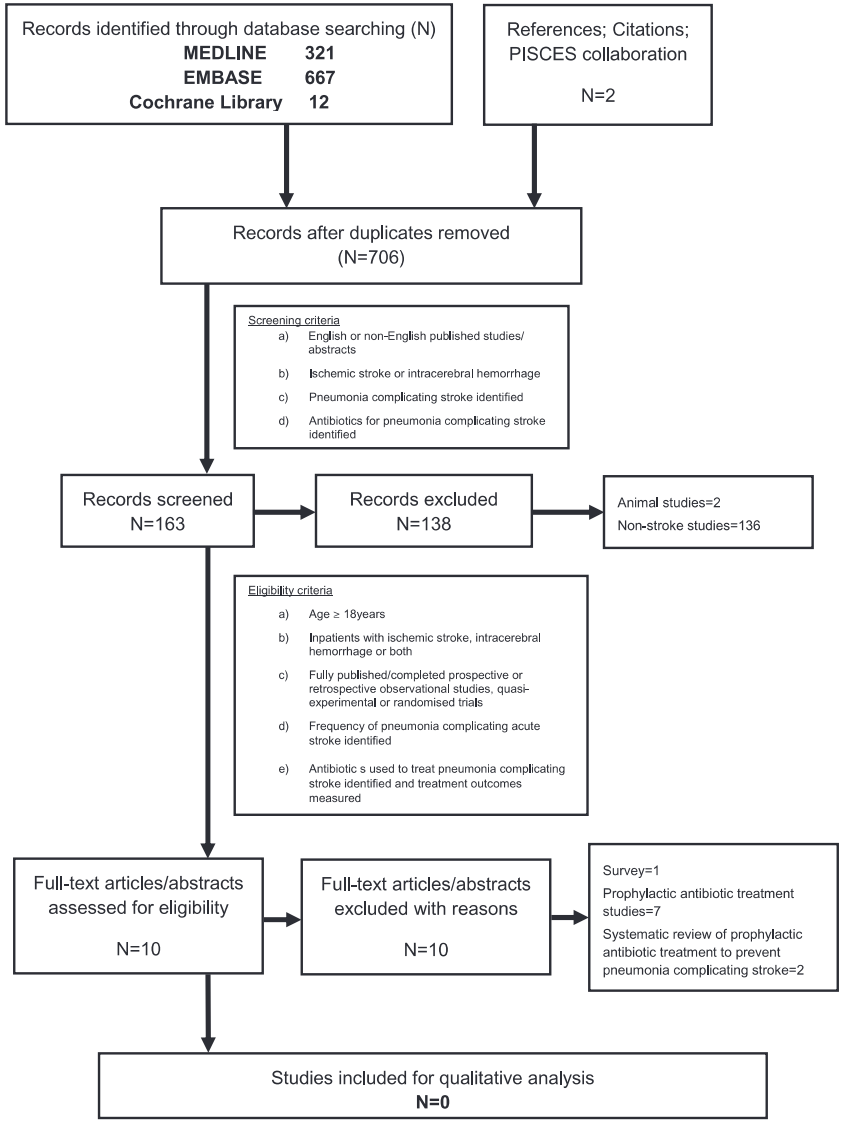


Figure 2. Flow diagram of systematic search methodology.

therapy is the cornerstone of the initial treatment of SAP, a standardised approach for clinicians initiating antibiotics could be a crucial component of antibiotic stewardship and improving clinical outcomes.

While there are existing specialist societal guidelines available for CAP and HAP, these do not necessarily

antimicrobial coverage. Pneumonia preceding stroke onset is common[25] and when triggering, stroke onset may subsequently manifest as pneumonia soon after admission to hospital. While *S. pneumoniae*, the most frequent pathogen in CAP worldwide,[26] was detected infrequently in pneumonia complicating stroke in our

to organisms cultured are at best sparse, our consensus on antibiotic coverage was based on the concept that organisms in early SAP would overlap most with those that of CAP and those of late SAP would also include those of HAP.

Pneumonia complicating stroke has conventionally been regarded as aspiration pneumonia in the setting of dysphagia and oro-pharyngeal aspiration and may be labelled as "aspiration pneumonia" in the stroke literature.[3] The microbial aetiology and potential antibiotic coverage of aspiration pneumonia are therefore of interest to clinicians treating pneumonia in dysphagic stroke patients. Micro-aspiration is in fact the primary pathophysiological process in both CAP and HAP with the latter characterised by micro-aspiration of colonised organisms in the hospital environment.[17] In recent years, the microbial aetiology of hospitalised aspiration pneumonia appears to be less dominated by anaerobes, and broad-spectrum antibiotics such as fluoroquinolones or β-lactams (e.g. carbapenems or penicillins plus β-lactamase inhibitors) are typically recommended for empirical treatment rather than targeted coverage of anaerobes.[17]

In adults hospitalised with CAP, fast antigen detection methods and real-time multibacterial and multiviral PCR platforms can increase the pathogen detection yield in sputum or endotracheal aspirate compared to conventional culture methods and could be used to better inform pathogen-directed antibiotic therapy.[27] Despite the recognised issue of reduced sputum availability in stroke patients, prospective studies of patients with suspected SAP employing more rigorous sampling, such as fiberoptic bronchoscopes in selected patients, and multiplex PCR are needed to further characterise microbial aetiology and validate empirical antibiotic recommendations. To our knowledge, viral pathogens have not been tested for in SAP or acute lower-respiratory tract syndromes complicating acute stroke, which may relate to availability of requisite molecular technology or perception that viral pneumonia does not align with the traditional paradigm of "aspiration" pneumonia in patients with stroke.

We were unable to make definitive recommendations for specific antibiotic classes (or antibiotic agent may be important in SAP as antibiotics have varying antimicrobial coverage and pleiotropic effects independent of their bactericidal or bacteriostatic effects. Several antibiotics (e.g. macrolides, cephalosporins, fluoroquinolones) commonly used to treat SAP have protective or deleterious effects in experimental middle cerebral artery occlusion[28–31] often via anti-inflammatory and immunomodulatory effects.

Our consensus statement proposes practical recommendations on antibiotic use in pneumonia complicating stroke, by experts within the PISCES group, using a modified Delphi approach. Our recommendations were not commissioned guidelines and hence should not be considered as a clinical guideline as this would not only require an adapted methodology (for example, PICO questionnaire framework and/or Levels of quality/expression of strength of recommendations) but would also need to cover other preventative and therapeutic strategies relevant to pneumonia complicating stroke, which is beyond the scope of the present work. However, this consensus provides the framework for a SAP guideline, which is in line with previous work from the PISCES group dealing with SAP.[3,4]

Conclusion

Consensus opinion is proposed on antibiotic treatment for the spectrum of pneumonia complicating stroke. However, large-scale RCTs are required to evaluate the efficacy and cost-effectiveness of specific antibiotic regimens for SAP, preferably with standardised diagnostic algorithms, rigorous microbiological testing and validation of severity scores and candidate biomarker panels to guide treatment initiation and cessation. Such RCTs will inevitably be challenging when considering the logistics around organisation of stroke services, regional and local site considerations (antibiotic costs, availability, susceptibility and resistance patterns, implementation issues) but are essential for informing evidence-based treatment for SAP and advancing our commitment to antibiotic stewardship in stroke unit care.

Declaration of Conflicting Interests

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Ethical approval

Not applicable

Informed consent

Not applicable

Guarantor

Amit K Kishore and Craig J Smith

Contributorship

CJS, AM, and JM developed the consensus protocol. AKK and CJS researched literature and performed the systematic reviews. AKK and CJS produced first draft of the manuscript. All authors were involved in the consensus process and in the production of the submitted manuscript.

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None

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References

1. Finlayson O, Kapral M, Hall R, et al. Canadian Stroke Network; Stroke Outcome Research Canada (SORCan) Working Group. Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. *Neurology* 2011; 77: 1338–1345.
2. Popovic N, Stefanovic-Budimkic M, Mitrovic N, et al. The frequency of poststroke infections and their impact on early stroke outcome. *J Stroke Cerebrovasc Dis* 2013; 22: 424–429.
3. Kishore AK, Vail A, Chamorro A, et al. How is pneumonia diagnosed in clinical stroke research? A systematic review and meta-analysis. *Stroke* 2015; 46: 1202–1209.
4. Smith CJ, Kishore AK, Vail A, et al. Diagnosis of stroke-associated pneumonia: recommendations from the pneumonia in stroke ConsEnsuS group. *Stroke* 2015; 46: 2335–2340.
5. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138–1180.
6. Hoffmann S, Harbison J, Hannay C, et al. Nosocomial infections in adult neurological patients: an analysis of risk factors in 1617 patients. *Int Care Med* 2004; 30: 2162–2168.
7. Harms H, Grittner U, Drenck NE, et al. Risk factors for poststroke pneumonia in hospitalized stroke patients with dysphagia. *J Neurol Neurosurg Psychiatry* 2012; 83: 1225–1230.
8. Kishore AK, Vail A, Jean AR, et al. Microbiological etiologies of pneumonia complicating stroke: a systematic review. *Stroke* 2018; 49: 1602–1609.
9. Chamorro A, Meisel A, Planas AM, et al. The immunology of acute stroke. *Nat Rev Neurol* 2012; 8: 401–410.
10. Meisel A and Smith CJ. Stroke preventive antibiotics for stroke-associated pneumonia. *Nat Rev Neurol* 2015; 11: 672–673.
11. Sadarangani SP, Estes LL and Steckelberg JM. Non-anti-infective effects of antimicrobials and their clinical applications: a review. *Mayo Clin Proc* 2015; 90: 109–127.
12. Shamseer L, Moher D, Clarke M, et al. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P): elaboration and explanation. *BMJ* 2015; 349: g7647.
13. Hasson F, Keeney S and McKenna H. Research guidelines for the Delphi survey technique. *J Adv Nurs* 2000; 32: 1008–1015.
14. Torres A, Niederman MS, Chastre J, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. *Eur Respir J* 2017; 50: 1700582.
15. American Thoracic Society. Guidelines for the management of adults with hospital-acquired ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care* 2005; 171: 388–416.
16. www.nice.org.uk/guidance/cg191/resources/pneumonia-in-adults-diagnosis-and-management-pdf-35109868127173 (accessed 18 December 2018).
17. DiBardino DM, Richard G and Wunderink RG. Aspiration pneumonia: a review of modern trends. *J Crit Care* 2015; 30: 40–48.
18. El-Solh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med* 2003; 167: 1650–1654.
19. Wang JL, Chen KY, Fang CT, et al. Changing bacteriology of adult community-acquired lung abscess in Taiwan: *Klebsiella pneumoniae* versus anaerobes. *Clin Infect Dis* 2005; 40: 915–922.
20. Tokuyasu H, Harada T, Watanabe E, et al. Effectiveness of meropenem for the treatment of aspiration pneumonia in elderly patients. *Intern Med* 2009; 48: 129–135.
21. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice

25. Grau AJ, Urbanek C and Palm F. Common infections and the risk of stroke. *Nat Rev Neurol* 2010; 6: 681–694.
26. Prina E, Ranzani OT and Torres A. Community-acquired pneumonia. *Lancet* 2015; 386: 1097–1108.
27. Gadsby NJ, Russell CD, McHugh MP, et al. Comprehensive molecular testing for respiratory pathogens in community-acquired pneumonia. *Clin Infect Dis* 2016; 62: 817–823.
28. Kim SY and Jones TA. The effects of ceftriaxone on skill learning and motor functional outcome after ischemic cortical damage in rats. *Restor Neurol Neurosci* 2013; 31: 87–97.
29. Becker KJ, Zierath D, Kunze A, et al. The contribution of antibiotics, pneumonia and the immune response to stroke outcome. *J Neuroimmunol* 2016; 295–296: 68–74.
30. Katayama Y, Inaba T, Nito C, et al. Neuroprotective effects of erythromycin on ischemic injury following permanent focal cerebral ischemia in rats. *Neurol Res* 2016; 38: 275–284.
31. Katayama Y, Inaba T, Nito C, et al. Neuroprotective effects of clarithromycin against neuronal damage in cerebral ischemia and in cultured neuronal cells after oxygen-glucose deprivation. *Life Sci* 2017; 168: 7–15.